Applied Organometallic Chemistry (1987) 1 227–234

0268–2605/87/01302227/$03.50

REVIEW

Germapharmaca:* some recent studies on biologically active organogermanium compounds

John S. Thayer
Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221, USA

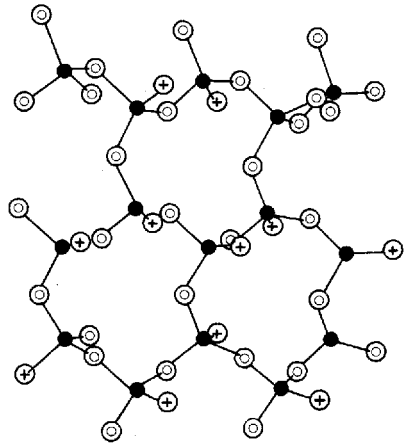
Received 29 May 1986 Accepted 14 June 1986

Recent research results on biologically active organogermanium compounds are described. Emphasis is placed on two categories based on (1) carbethoxyethylgermanium sesquioxide and (2) the 'spirogermanium' system. Other organogermanium derivatives covered include various mono-, di-, tri- and tetra-compounds. Mention is also made of organogermanium compounds as food additives and as the products of biological methylation.

INTRODUCTION

While biologically active organogermanium compounds have been known for many years,[1] they have become prominent enough to deserve a review only very recently. Some earlier work in this area has been included in a review of germanium compounds and their biological effects;[2] comparative toxicological studies have also been reported.[3] The roles of germanium compounds in agriculture and nature have likewise been reviewed.[4]

The currently surging research activity in organosilicon drugs[1,5,6] seems to be causing a similar interest in organogermanium compounds. However, one important difference must be noted: many biologically active organosilicon species are sila analogs of organic biochemicals; however, corresponding germa analogs are generally not known, making such materials a promising area for research. The majority of reported biological research on organogermanium species involves only two compounds: carboxyethylgermanium sesquioxide, $[(HO_2CCH_2CH_2Ge)_2O_3]_n$, **I**, and N-(3-dimethylaminopropyl)-2-aza-8, 8-diethyl-8-germaspiro[*4.5*]decane ('spirogermanium'; NSC-192965) **II**. Derivatives or analogs of **I** account for much of the remainder.



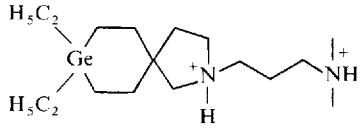
I

● = Ge; ⊙ = O; ⊕ = $HO_2CCH_2CH_2$

Two other unique aspects of current research in biologically active organogermanium compounds are: (1) the majority of reports have emphasized the uses or potentialities of such compounds specifically as antitumor agents, although there are certainly other medicinal applications that show great promise; (2) the great majority of this work has been done in Japan, often under the aegis of The Asai Germanium Research Institute or The Tokuyama

*The Greek word *pharmakon* can mean either a medicine or a poison. The term 'germapharmaca' incorporates both meanings, and refers to any organogermanium compound showing biological activity. Tacke uses a corresponding term 'silapharmaca' in a more restricted sense, applying it specifically to sila analogs of oganic drugs.[7,8]

Soda Company. Germanium-containing health foods also appear in Japan.



II

MONOORGANOGERMANIUM SESQUICHALCONIDES

Carboxyethylgermanium sesquioxide

General properties

This compound is a white solid that remains unchanged when heated up to 320°.[2,9] It is highly polymeric in the solid state, and is insoluble in common organic solvents, but in aqueous solution the following equilibrium probably exists:[9]

$$[(RGe)_2O_3]_n + 3n\,H_2O \leftrightharpoons 2n\,RGe(OH)_3 \qquad [1]$$

$$R = -CH_2CH_2CO_2H.$$

The solid state structure resembles that of metasilicates and of crown ethers; one paper suggested[9] that at least part of the biological activity of I arises from its ability to form complexes with metal ions.

Antitumor properties

Much of the earlier research on the antitumor activity of I has been reviewed elsewhere.[2] At present, the current research still involves laboratory animals (primarily mice). In one such report, mice that had been innoculated with Lewis lung carcinoma were treated with I.[10] Results depended on the time of administration; treatment on day 1 caused 47% inhibition, but treatment on day 8 actually enhanced tumor growth.[10] Doses of I ($100\,mg\,kg^{-1}\,day^{-1}$) inhibited Ehrlich ascites tumors in mice.[11] In a very interesting development, serum removed from mice suffering from various ascites tumors which had been treated with I showed antitumor activity when administered to other mice.[12]

The reason for the antitumor activity of I (and its derivatives) has not been determined. Recent reports[10,12] suggest that it may act through stimulation of the immune system, rather than by direct attack on the tumor itself. Such effects of I on the immune system are discussed in the following section.

Immunological applications

Earlier work involving I suggested that this compound acted as an immune adjuvant,[1,2] and more recent work has confirmed these findings. When administered to ageing mice with decreased immunity, I normalized the immune response.[13] The same compound reversed the suppression of γ-interferon in thermally injured mice.[14] Doses of $300\,mg\,kg^{-1}$ enhanced the natural killer cell activity and interferon levels in mice.[15]

When combined with mitomycin C, I showed an immune adjuvant effect in mice that had been innoculated with L-1210 tumor cells.[16] Oral administration of I to mice activated their peripheral macrophages; these, when cultivated with leukemia or Ehrlich carcinoma cells, markedly suppressed the growth of the latter.[16] The author suggested that the antitumor activity of I might result from activation of macrophage.[17] Combination of I with indomethacin enhanced the latter as an immunostimulating agent.[18,19]

Other biological uses

Administration of I to rats resistant to morphine altered their pain threshhold and sensitized them to morphine.[20] It also enhanced the analgesic effects of morphine.[21] Oral administration of I at $100\,mg\,kg^{-1}\,day^{-1}$ for 8 days to rats with chronic respiratory disease markedly decreased the number of *Mycoplasma pulmonis* in nasal fluid.[22]

The lithium salt of I was reported to have an LD_{50} value of $2700\,mg\,kg^{-1}$ in mice over a 24-hour period.[23] Salts of I prevented the denaturation of carp myosin at low temperatures.[24]

Derivatives of Carboxyethylgermanium sesquioxide

Definition

Many derivatives of I have been prepared and investigated. In fact, much recent work has concentrated on these derivatives rather than the parent compound. Derivatives of this compound are considered to be formed through replacement of one of the ethyl hydrogens by an organic group, or replacement of the hydroxyl group by an amino group to form an amide. These latter

derivatives are the most common. Compounds analogous to **I** are discussed in the next section.

Antitumor properties

The amide $[C_6H_5CH_2CH(CO_2C_2H_5)NHC(:O)CH_2CH_2Ge]_2O_3$ was active against IMC carcinoma in mice,[25] as were the amides $[RNHC(:O)CH_2CH(CH_3)Ge]_2O_3$, when given to mice at doses of $2\,mg\,kg^{-1}$ daily, reduced IMC tumor weight by 56%,[27] and also proved to be effective against solid IMC tumor.[28]

Bacteriostatic properties

Although certain organogermanium compounds are known to show bactericidal or bacteriostatic activity,[1,2] this has been little studied for **I** or its derivatives. Compounds such as $[RNHC(:O)CH_2CH(C_6H_5)Ge]_2O_3$ (where R is a β-lactam) inhibit the growth of *Staphylococcus aureus*, *S. epidermis* and related species.[29]

Analogs of Carboxyethylgermanium sesquioxide

Definition

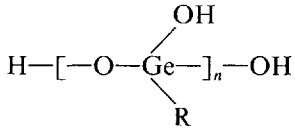
The parent compound **I** may be divided into three parts: the organic group, the germanium atom, and the oxygen atoms. Any part might be replaced to give an analog, and most such analogs retain biological activity. The great majority of such compounds have been investigated for their antitumor capabilities.

Organogermanium sesquioxides

These have the general formula $[(RGe)_2O_3]_n$. Compounds in which R = uracil[30] or 5-fluorouracil[31] (5-fluorouracil itself is used in treatment of certain types of cancer) showed activity against IMC carcinoma in mice. *p*-Fluorophenylgermanium sesquioxide, in tablet form, acted against Ehrlich ascites tumor in mice.[32] Other substituted phenylgermanium sesquioxides likewise displayed antitumor activity.[33] The homolog 2-carboxypropylgermanium sesquioxide gave 80% inhibition of B_{16} melanoma in mice and dogs.[34] Doubtlessly additional such materials will be synthesized and investigated for their biological activity, not only against cancer but also against other bodily ailments.

Monoorganogermanium trihydroxides and derivatives

In aqueous media, I and its derivatives probably exist primarily as the trihydroxides $RGe(OH)_3$. A few attempts have been made to prepare distinct compounds $RGeX_3$ (X = OH, OR', halide, etc.) for testing. Polymeric species of formula

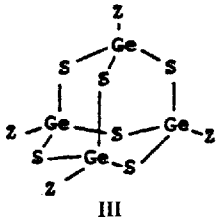


(R = substituted carboxyethyl group; $n \geqq 3$) act as antitumor agents at doses of 50–200 $mg\,kg^{-1}$ in mice.[35] Substituted phenylgermanium trialkoxides also showed activity against tumors in mice,[36] although these may have been partially hydrolyzed.

Organogermanium sesquisulfide

Various compounds of formula $(RGe)_2S_3$ have been reported. The parent compound, carboxyethylgermanium sesquisulfide, differs appreciably from its oxygen counterpart.[37] This compound melts at 200°, exists as a tetramer and has the structure **III**. Numerous derivatives have been reported as well.[37] These show 'more efficacious antitumor activity' than the corresponding oxy derivatives, and stronger action as a pain reliever.[37] The 1,1-dimethyl derivative of **III** showed an antoxidant activity comparable to that of Vitamin E.[37] The 1-phenyl derivative, at levels of $25\,mg\,kg^{-1}$, caused 56% inhibition of IMC carcinoma in mice.[38] Oral administration of the corresponding amide likewise inhibited IMC carcinoma, possibly by modification of the immune mechanism.[39]

Antibacterial activity has also been reported for **III** and various derivatives.[40] At levels of $1\,\mu g\,cm^{-3}$, **III** caused 76.4% inhibition of dipeptidylcarboxypeptidase enzyme.[37,41]



III

($Z = HO_2CCH_2CH_2$)

Monoorganosilicon sesquioxides

Several silicon analogs of **I** have been reported. The mixed species $(HO_2CCH_2CH_2Si_xGe_{1.00-x})_2O_3$

($x = 0.05$–1.00) show antitumor activity,[42] although there was no indication whether the extent of such activity depended on the Si/Ge ratio. Compounds of general formula $[R(CH_3)C=NCH_2CH_2CH_2Si]_2O_3$ have been tested for their anticancer properties. For R = phenyl, interperitoneal doses of 25 mg kg^{-1} prolonged survival times by 235% for mice having Ehrlich ascites tumors.[43] Under similar conditions, the *p*-cyanophenyl compound at doses of 400 mg kg^{-1} gave a 200% increase in survival time.[44] Various furfuryl derivatives also showed antitumor activity.[45] It might be noted that these compounds all have a Si—C—C—C—N framework, which has been found to cause biological activity in many organosilicon compounds.[1] However, antitumor activity was also found in 5-fluorouracil derivatives of silsesquioxides where such a linkage does not exist.[46]

The observed activity of these silicon compounds raises the question as to how important the germanium atom in **I** or **III** happens to be. On the basis of currently available information, the polymeric structure seems to be the crucial factor, suggesting that exchange of silicon for germanium (or any other quadrivalent element) might make little difference if the structure is not markedly altered. In this context, it is worth noting that both **I** and its silicon analog stimulated the growth of rice seedlings.[47–49] Preliminary results seemed to indicate that the tertiary structure of the silicon compound was necessary for its activity.[50] One can but wonder whether corresponding derivatives of tin or phosphorus would show corresponding activity.

SPIROGERMANIUM

Origins and properties

This compound was originally prepared as part of an ongoing study of azaspirans.[51] It is a high-boiling liquid. While a variety of derivatives and analogs are known, the dihydrochloride (m. 287–8°), **II**, is the compound actually used in anticancer studies. Much of the research involving **II** has recently been reviewed.[52,53]

Anticancer research

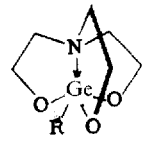
At the time of this writing, most of the research involving **II** has concentrated on tests in animals, although a few clinical trials have also appeared.[52] It has shown activity against many varieties of cancer cells, though not against all. For example, **II** decreased the percentage of donor-type lymphoma metaphase cells in mice[54] and was active against pancreatic adenocarcinoma cells.[55] It was active against lymphoma L5178Y cells that were resistant to 5-fluorouracil.[56]

Investigations on hamster cells indicated that **II** was cytotoxic,[57,58] with toxicity depending on dose,[57,58] exposure time[57] and temperature.[57] While it affected rat neurons,[57] **II** was not toxic to hemapoietic stem cells in mice.[59] Spirogermanium showed no toxicity towards bone marrow, but did display reversible central nervous system toxicity.[60] Finally, **II** showed in vitro activity against *Plasmidium falsiparum*, thereby suggesting antipaludistic activity.[61]

OTHER ORGANOGERMANIUM COMPOUNDS

Monoorganogermanium compounds

Carbethoxygermanium sesquioxide, along with its derivatives and analogs, comprises the major examples of bioactive monoorganogermanium compounds. The only other examples are a few germatranes, **IV**. One such compound, with R = —$CH_2CH_2C(:O)NH_2$ (note the structural similarity to **I**), showed activity against IMC carcinoma in mice.[62] Administration of 3-(1-germatranyl)propionic acid to mice afflicted with Ehrlich ascites tumor caused a 78% increase in survival time.[34] Germatranes with substituents in the 5-position showed antitumor activity.[63]

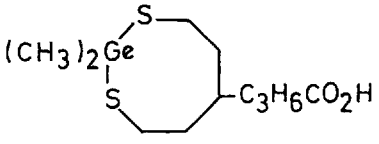


IV

Di- and triorganogermanium compounds

Little systematic work has been done on compounds in this category. Compound **V** and its diethylgermyl analog are reported to be effective antitumor, antiinflammatory and antiinfective agents.[64] Incorporation of a methylphenylgermyl group into a porphyrin system resulted in a R_2GeN_4 structure that showed activity against

carcinoma in mice.[65] An organogermanium analog of cysteamine had both higher radioprotective power and greater toxicity than cysteamine itself.[66] Di-*n*-butylgermanium dichloride decreased antibody production by lymphocytes and induced mutation in Chinese hamster ovary cells.[67] Comparative cytotoxicity studies on L-1210 mouse leukemia cells indicated that triphenylgermanium chloride was appreciably less toxic than its tin or lead counterparts.[68]



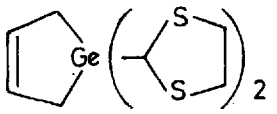
V

Tetraorganogermanium compounds

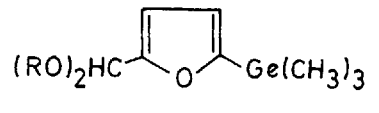
Symmetrical tetraorganogermanium compounds show no biological activity.[2] The most commonly reported unsymmetric molecule having a C_4Ge framework is the previously discussed spirogermanium, **III**. The germacyclopentene derivative **VI** has been reported to be more potent against IMC carcinoma in mice than carboxyethylgermanium sesquioxide.[69] Certain trimethylgermyl compounds show antitumor activity. The furan derivative, **VII**, acted against Lewis lung carcinoma and melanoma B_{16}.[70] Various compounds of the general formula

$$R_3Ge(CH_2)_mNHC(:O)N(CH_2)_nX$$
$$\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\quad NO$$

(X = halide; $m, n = 2, 3$) proved to be anticancer agents in mice at levels of 12.5–50 mg kg^{-1}.[71] The



VI



VII

related compound $(C_2H_5)_3GeCH_2CH_2CH_2N{=}CHC_6H_4Br$-*p* prolonged the survival of mice having Ehrlich ascites carcinoma by 78%.[72]

ORGANOGERMANIUM COMPOUNDS AS FOOD ADDITIVES

Germanium dioxide has been reported in certain plants that are used for medicinal purposes, and has also been used as an additive for nutritional purposes.[2] Organogermanium compounds have been used for the same purposes. Honeybees fed diluted honey containing polymeric $[(CH_3)_2GeO]_x$ produced honey enriched in germanium usable as a health food.[73] Similar results occurred when bees were fed aqueous solutions of **I** with sucrose.[74] Carbonated soft drinks containing **I** have also been reported.[75] Addition of **I** to fermented vinegar gives a health drink that is claimed to enhance induction of interferon and to have a antidiabetic effect.[76] When **I** or its sodium salt were added to poultry feed, the fowls produced germanium-enriched eggs that were claimed to be health foods.[77] Aqueous solutions of **I** were used with dough to produce germanium-enriched noodles.[78] Cultivation of *Saccharomyces cerevisiae* in a germanium-containing medium gave yeast containing 550 μg g^{-1} germanium;[79] when this was included in the diet of mice, the incidence of methylcholanthrene-induced tumors decreased significantly. Addition of an (unspecified) organogermanium compound increased the storage stability of sugars.[80]

BIOLOGICAL FORMATION OF METHYLGERMANIUM COMPOUNDS

Work reported in the preceding section indicates that both hydrated germanium dioxide, probably $Ge(OH)_4$, and **I** can be taken up by certain organisms. Whether they undergo any transformation is not known. There have been a number of reports of methylgermanium compounds occurring in natural waters.[1,81–84] Concentrations of CH_3GeX_3 and $(CH_3)_2GeX_2$ in sea water have been reported at levels of 330 ± 15 and 120 ± 20 picomolar respectively; no $(CH_3)_3GeX$ species were detected.[82] These methylgermanium compounds behave 'conservatively', their concen-

trations not being affected by a 'spring bloom' of diatoms in Charlotte Harbor, Florida (USA),[83] nor did they enter the biogeochemical cycle of silicon.[82] This is a distinct contrast to $Ge(OH)_4$, which can be taken up along with dissolved silicates; in fact, Ge-68 has been used as a radioactive tracer in the study of silicon metabolism.[2] Concentrations of methylgermanium compounds increased linearly with increasing salinity.[83]

Since methylgermanium compounds are not used commercially, these methylgermanium species in natural waters must form through biological methylation—a process well known for mercury, tin, arsenic and various other elements.[1,85] No direct observations on the biomethylation of germanium have been reported, but methylation of tin compounds occurs in natural sediments through microbial action,[1,85] and it is reasonable to suppose that germanium can be methylated in the same way.

CONCLUSIONS AND DISCUSSION

'Germapharmaca', as an entity, stands very much in its infancy. The research that has appeared, while extensive, still leaves many questions unanswered and generates many tantalizing possibilities. The role of the germanium atom itself is uncertain. The similarity of the sila- and germa-derivatives of type $(HO_2CCH_2CH_2E)_2O_3$ suggests that the basic structural unit itself, rather than the silicon or germanium, may be the primary source of reported biological activity. The antitumor activity apparently derives from these compounds' stimulatory effect on the immune system of the host organism—an approach that is becoming increasingly important in cancer research.[86] The mechanism of this immune adjuvant activity has still not been established. Potentially, I and related compounds may find therapeutic uses well beyond their current uses as anticancer drugs, especially in body disorders arising from deficiencies in the immune system.

The position in the Periodic Table indicates that germanium will have chemical resemblances both to silicon and to tin. Thus far, the organogermanium compounds used as drugs have resembled their silicon analogs, as illustrated by both I and germatranes. The silicon analog of spirogermanium, at concentrations of $10\,\mu g\,cm^{-3}$, inhibited human cancer cell growth.[87] This also suggests that perhaps other germa analogs of organic and organosilicon pharmaceuticals will show biological activity—a research area that has received very little attention to date.

Metabolic pathways of organogermanium compounds presently remain almost entirely unknown. Two recent papers[88,89] report that catechol facilitated the intracellular accumulation and distribution of GeO_2 by *Pseudomonas putida* cells. The existence of methylgermanium compounds in natural waters strongly implies biomethylation, which in turn indicates a resemblance of germanium to tin in this particular area of chemistry. The existence of various germanium-containing 'health foods' suggests, rightly or wrongly, that at least certain germanium compounds may be beneficial to human health. In this context, it might be noted that silicon is known to be a micronutrient, required for good health, and a book has just appeared which suggests that tin might also be a micronutrient.[90] Thus, the rather fragmentary evidence currently available raises the question as to whether germanium compounds might also be micronutrients. This question can only be settled, one way or the other, by more, sustained research. In fact, the whole area of 'germapharmaca' appears to be extremely promising for research results, and many more developments may be expected from it in years to come.

REFERENCES

1. Thayer, JS *Organometallic Compounds and Living Organisms*, Academic Press, 1984
2. Thayer, JS *Rev. Silicon, Germanium, Tin & Lead Comp.*, 1985, 8: 133
3. Sandhu, GK and Sandhu, GK *J. Chem. Sci.*, 1983, 9: 36; *Chem. Abs.*, 1985, 103: 33078e
4. Takahashi, E *Nogyo oyobi Engei*, 1985, 60: 1197; *Chem. Abs.*, 1985, 103: 208971v
5. Fessenden, RJ and Fessenden, JS In: *Advances in Organometallic Chemistry*, Stone, FGA and West, R (eds), Academic Press, New York, 1980, 10: 275
6. Tacke, R In: *Organosilicon and Bioorganosilicon Chemistry*, Sakurai, H (ed), Halsted Press, New York, 1985, p 251
7. Tacke, R, Bentlage, A, Towart, R and Moeller, E *Eur. J. Med. Chem.—Chim. Ther.*, 1983, 18: 155; *Chem. Abs.* 1983, 99: 38524f
8. Sheldrick, W.S., Linoh, H, Tacke, R, Lambrecht, G, Moser, U and Mutschler, E *J. Chem. Soc., Dalton Trans.*, 1985, 1743; *Chem. Abs.*, 1986, 104: 109758v

9. Tsutsui, M, Kakimoto, N, Axtell, DD, Oikawa, H and Asai, K *J. Am. Chem. Soc.*, 1976, 98: 8287; *Chem. Abs.*, 1977, 86: 10964g
10. Kumano, N, Ishikawa, T, Koinumara, S, Kikumoto, T, Suzuki, S, Nakai, Y and Konno, K *Tohodu J. Exp. Med.*, 1985, 146: 97; *Chem. Abs.*, 1985, 103: 153475d
11. Sato, R *Chem. Abs.*, 1984, 100: 151043a
12. Suzuki, F, Brutkiewicz, RR and Pollard, RB *Brit. J. Cancer*, 1985, 52: 757; *Chem. Abs.*, 1986, 104: 392v
13. Mizushima, Y, Watanabe, H, Yoko, S, Yanagawa, A and Hoshi, K *Chem. Abs.*, 1982, 99: 119984s
14. Suzuki, F and Pollard, RB *J. Interferon Res.*, 1984, 4: 223; *Chem. Abs.*, 1985, 103: 47935u
15. Aso, H, Suzuki, F, Yamaguchi, T, Hayashi, Y, Ebina, T and Ishida, N *Microbiol. Immunol.*, 1985, 29: 65; *Biol. Abs.*, 1985, 79: 89141
16. Arimori, S, Watanabe, K, Yoshida, M and Nagao, T *Chem. Abs.*, 1982, 97: 156062k
17. Suzuki, F *Chem. Abs.*, 1986, 104: 45447h
18. Shoji, Y, Mizushima, Y, Sakagami, A and Miyao, K *Int. J. Immunother.*, 1985, 1: 99; *Chem. Abs.*, 1986, 104: 141918h
19. Shoji, Y, Sakagami, A and Mizushima, Y *Int. J. Immunother.*, 1985, 1: 215; *Chem. Abs.*, 1986, 104: 1419221d
20. Asai Germanium Research Institute, *Chem. Abs.*, 1983, 99: 187743d
21. Hachisu, M, Takahashi, H, Koeda, T and Sekizawa, Y *J. Pharmacabio.-Dyn.*, 1983, 6: 814; *Biol. Abs.*, 1984, 77: 5911
22. Sato, R *Chem. Abs.*, 1984, 100: 151041y
23. Wiese, U, Frenzel, G and Biel, Aa *Chem. Abs.*, 1984, 100: 85930j
24. Kakimoto, N and Shinano, H *Chem. Abs.*, 1986, 104: 108224f
25. Asai Germanium Research Institute, *Chem. Abs.*, 1984, 101: 111205u
26. Asai Germanium Research Institute, *Chem. Abs.*, 1984, 101: 171516f
27. Asai Germanium Research Institute, *Chem. Abs.*, 1985, 103: 22789m
28. Asai Germanium Research Institute, *Chem. Abs.*, 1985, 102: 143179a
29. Asai Germanium Research Institute, *Chem. Abs.*, 1983, 99: 139643z
30. Asai Germanium Research Institute, *Chem. Abs.*, 1984, 101: 91237a
31. Asai Germanium Research Institute, *Chem. Abs.*, 1984, 101: 152092y
32. Tokuyama Soda Co., *Chem. Abs.*, 1984, 101: 216415r
33. Tokuyama Soda Co., *Chem. Abs.*, 1985, 103: 204107z
34. Lukevits, EY, Germane, SK, Zidermane, AA, Dauvarte, AZ, Kravchenko, IM, Trushule, MA, Moronov, VF, Gar, TK, Khromova, NY *et al.*, *Khim.-Farm. Zh.*, 1984, 18: 154; *Biol. Abs.*, 1985, 79: 32848
35. Kakimoto, N *Chem. Abs.*, 1983, 98: 16856t
36. Tokuyama Soda Co., *Chem. Abs.*, 1985, 102: 204108a
37. Kakimoto, N, Matsui, M, Takada, T and Akiba, M *Heterocycles*, 1985, 23: 2681
38. Kakimoto, N, Tanaka, N, Miyao, K and Ohnishi, T *Chem. Abs.*, 1985, 103: 37622a
39. Sato, I, Yuan, BD, Nishimura, T and Tanaka, N *J. Biol. Resp. Modif.*, 1985, 4: 159; *Chem. Abs.*, 1985, 103: 64443z
40. Kakimoto, N, Katayama, T and Hazato, T *Chem. Abs.*, 1983, 98: 215805a
41. Kakimoto, N, Katayama, T and Hazato, T *Chem. Abs.*, 1985, 103: 22787j
42. Sato, T *Chem. Abs.*, 1981, 95: 81219q
43. Tokuyama Soda Co., *Chem. Abs.*, 1984,, 100: 151043a
44. Tokuyama Soda Co., *Chem. Abs.*, 1984, 101: 17328q
45. Kato, S *Chem. Abs.*, 1986, 104: 75011d
46. Tokuyama Soda Co., *Chem. Abs.*, 1985, 102: 67393y
47. Kakimoto, N and Miyao, K *Chem. Abs.*, 1980, 92: 146913w
48. Kakimoto, N and Miyao, K *Chem. Abs.*, 1980, 92: 198527t
49. Kakimoto, N and Miyao, K *Chem. Abs.*, 1985, 103: 118259q
50. Harada, J *Chem. Abs.*, 1985, 103: 137070n
51. Rice, LM, Wheeler, JM and Geschickter, CF *J. Heterocycl. Chem.*, 1974, 11: 1041; *Chem. Abs.*, 1975, 82: 112146b
52. Atassi, G *Rev. Sil. Germ. Tin Lead Compds.*, 1985, 8: 219; *Chem. Abs.*, 198?
53. Slavik, M, Blanc, O and Davis, J *Invest. New Drugs*, 1983, 1: 225; *Chem. Abs.*, 1983, 99: 205376t
54. Schwartz, GN, Biegel, JA and Boggs, SS *Leukemia Res.*, 1982, 6: 269; *Biol. Abs.*, 1983, 75: 19969
55. Chang, BK *Cancer Treatm. Rep.*, 1983, 67: 355; *Biol. Abs.*, 1984, 77: 12978
56. Hill, BT *J. Nat. Cancer Inst.*, 1983, 71: 35; *Biol. Abs.*, 1984, 77: 69154
57. Hill, BT, Whatley, SA, Bellamy, AS, Jenkins, LY and Whelan, RDH *Cancer Res.*, 1982, 42: 2852; *Biol. Abs.*, 1983, 76: 4620
58. Yang, SJ and Rafla, S *Am. J. Clin. Oncol.*, 1983, 6: 331; *Biol. Abs.*, 1984, 77: 61067
59. Schwartz, GN, Biegel, JA, Fisher, B and Klein, I *Proc. Soc. Exp. Biol. Med.*, 1983, 173: 176; *Biol. Abs.*, 1984, 77: 77089
60. Slavik, M, Mrema, EJ and Saiers, JH *Drugs Under Exp. Clin. Res.*, 1982, 8: 379; *Biol. Abs.*, 1984, 77: 61066
61. Mrema, EJ, Slavik, M and Davis, J *Int. J. Clin. Pharm. Therap. Tox.*, 1983, 214: 167
62. Asai Germanium Research Institute, *Chem. Abs.*, 1984, 101: 91238b
63. Kakimoto, N, Sato, K, Takada, T and Akiba, M *Biol. Abs.*, 1985, 80: 97226
64. Sumitomo Chemical Co., *Chem. Abs.*, 1985, 103: 71513a
65. Sumitomo Chemical Co., *Chem. Abs.*, 1985, 103: 183556y
66. Satge, J, Cazes, A, Bouchaut, M and Fatome, M *Eur. J. Med. Chem.-Chim. Ther.*, 1982, 17: 433; *Chem. Abs.*, 1983, 98: 54061n
67. Li, AP, Dahl, AR and Hill, JO *Toxicol. Appl. Pharmacol.*, 1982, 64: 482; *Chem. Abs.*, 1982, 97: 157807u
68. Yamamoto, Y, Numasaki, Y and Murakami, M *Chem. Abs.*, 1985, 103: 47866x
69. Asai Germanium Research Institute, *Chem. Abs.*, 1985, 103: 22788k

70. Lukevits, EY, Ignatovich, LM, Zidermane, AA and Dauvarte, AZ *Chem. Abs.*, 1984, 101: 211311a
71. Tokuyama Soda Co., *Chem. Abs.*, 1986, 104: 50981g
72. Kato, S and Okamoto, H *Chem. Abs.*, 1986, 104: 149170d
73. Kimura, M and Kondo, K *Chem. Abs.*, 1982, 97: 143599r
74. Kondo, K, Kondo, A and Kondo, K *Chem. Abs.*, 1983, 98: 52271g
75. KI Kagaku KK *Chem. Abs.*, 1984, 100: 208208q
76. Reform System KK *Chem. Abs.*, 1985, 103: 70130m
77. Hochido, Y *Chem. Abs.*, 1985, 102: 112123y
78. Ogata, I *Chem. Abs.*, 1986, 104: 128628u
79. Kehlbeck, H *Chem. Abs.*, 1985, 103: 159136r
80. Kondo, K and Kondo, A *Chem. Abs.*, 1984, 101: 212993e
81. Andreae, MO and Froehlich, PN *Tellus* 1984, 36B: 101; *Chem. Abs.*, 1984, 101: 43221u
82. Lewis, BL, Froehlich, PN and Andreae, MO *Nature*, 1985, 313: 303; *Chem. Abs.*, 1985, 102: 119151q
83. Froehlich, PN, Kaul, LW, Byrd, JT, Andreae, MO and Roe, KK *Estuar. Coastal Shelf Sci.*, 1985, 20: 236; *Biol. Abs.*, 1985, 80: 48171
84. Mortlock, RA and Froehlich, PN *Science*, 1986, 231: 43
85. Thayer, JS and Brinckman, FE In: *Advances in Organometallic Chemistry*, Stone, FGA and West, R (eds), Academic Press, New York, 1985, 20: 314
86. Marx, JL *Science*, 1985, 230: 1367
87. Rice, LM, Sheth, BS and Wheeler, JW *J. Heterocycl. Chem.*, 1973, 10: 737; *Chem. Abs.*, 1974, 80: 14884r
88. Chmielowsky, J and Klapcinska, B *Appl. Environment. Microbiol.*, 1986, 51: 1099
89. Klapcinska, B and Chmielowsky, J *Appl. Environment. Microbiol.*, 1986, 51: 1144
90. Cardarelli, NF (ed), *Tin as a Vital Nutrient*, CRC Press, Boca Raton (FL; USA), 1986